been controlled by atrial overdrive pacing and mitral valve replacement.

GARY L. KISSEL, MD
J. MICHAEL CRILEY, MD

REFERENCES

Barlow JB, Pocik WA: The problem of nonejection systolic clicks and associated mitral systolic murmur—Emphasis on the billowing mitral leaflet syndrome. Am Heart J 90:636-655, Nov 1975

Criley JM, Lewis KB, Humphries JO, et al: Prolapse of the mitral valve. Clinical and cineangiographic findings. Brit Heart J 28:488-496, Jul 1966

Hancock EW, Cohn K: The syndrome associated with mid-systolic click and late systolic murmur. Amer J Med 41:183-196, Aug 1966

Criley JM, Kissel GL: Prolapse of the mitral valve: The click and late systolic murmur syndrome, chap 4, *In* Yu PN, Goodwin JF (Eds): Progress in Cardiology. Philadelphia, Lea & Febiger, 1975, pp 23-36

Treatment of Myxedema and Myxedema Coma

EXCEPT FOR myxedema coma, there are few situations in which hypothyroidism requires rapid restoration of the eumetabolic state. Hypothyroid patients are sensitive to thyroid hormone replacement, even at low doses and, therefore, therapy should be initiated at a dosage of no more than 50 μg of levothyroxine per day. In patients with underlying heart disease or severe hypothyroidism the initial daily dose should be even lower. The dose should then be increased by 25 to 50 μg at two- to four-week intervals until a normal metabolic state is reached. The final maintenance dose should be approximately 200 μg per day.

Occasionally, cardiovascular or psychiatric complications limit the use of the full therapeutic dose and replacement therapy must be modified to attain the maximal metabolic state without adverse effects.

The clinical state of the patient is generally the best determinant of adequate thyroid hormone replacement. The wide range of normal for thyroxine (T_4) concentration makes the T_4 determination useful only as a confirmation of a patient's metabolic state. In a patient with thyroprival hypothyroidism, thyroid-stimulating hormone (TSH) determinations can be used to assess the patient's response to thyroid hormone replacement.

Although levothyroxine appears to be the agent of choice in replacement therapy of hypothyroidism, for those who prefer other agents the equivalent doses are levothyroxine, 100 μg; liothyronine, 25 μg, and thyroid extract, 60 mg.

The severity of myxedema coma requires that the diagnosis be made clinically and therapy begun immediately. Therapy should be initiated with 400 to 500 μg of levothyroxine given intravenously. Respiratory care is critical and hypoventilation should be treated by assisted ventilation and controlled oxygen administration. The occasional associated hypoglycemia should be treated with concentrated glucose solutions to avoid water intoxication. Dilutional hyponatremia should be treated by water restriction but may occasionally require hypertonic saline infusion. Hydrocortisone, 100 to 200 mg per day, should be administered intravenously. The patient should not be actively warmed. Precipitating factors such as infection should be sought and treated.

Although myxedema coma generally has a poor prognosis, a regimen such as the above, especially with critical attention to respiratory care and ideally in the setting of an intensive care unit, should increase survivals.

ITAMAR B. ABRASS, MD

REFERENCES

Green WL: Guidelines for the treatment of myxedema. Med Clin North Am 52:431-450, Mar 1968

Stock JM, Surks ML, Oppenheimer JH, et al: Replacement dosage of L-thyroxine in hypothyroidism. N Engl J Med 290: 529-533, Mar 7, 1975

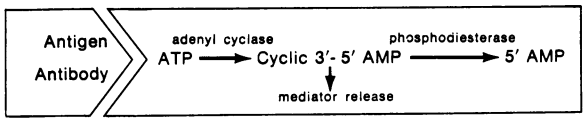
Holvey DN, Goodner CJ, Nicoloff JT, et al: Treatment of myxedema coma with intravenous thyroxine. Arch Intern Med 113:89-96, Jan 1964

Royce PC: Severely impaired consciousness in myxedema—A review. Am J Med Sci 261:46-50, Jan 1971

Bronchodilator Pharmacology

ALTHOUGH A VARIETY of catecholamine and xanthine preparations have been used for the treatment of asthma and other types of airway obstruction for many years, only recently has the mechanism of action of these agents become appreciated. An understanding of bronchodilator pharmacology has led to the rational use of these agents and has given impetus to the search for additional agents with greater specificity of action.

The airway obstruction of acute bronchial asthma is due, at least in part, to the release of several biologically active substances, as shown in a simplified diagram in Figure 1.



AMP = adenosine monophosphate
ATP = adenosine triphosphate

Figure 1.—Diagram showing release of biologically active substances.

Intracellular biochemical events are initiated by an antigen-antibody reaction on the cell surface, leading to a release of a variety of mediator substances. The level of cyclic adenosine monophosphate (AMP) inversely determines the amount of mediator release. Increased cyclic AMP leads to less mediator release and less bronchospasm, and decreased cyclic AMP leads to increased mediator release.

Among the agents that stimulate cyclic AMP formation, via the enzyme adenyl cyclase, are the beta-adrenergic stimulator agents (isoproterenol, metaproterenol, isoetharine and ephedrine), parasympathetic nervous system inhibitors and alpha-adrenergic blocking agents. A subgroup of beta-adrenergic agents (called beta-2) have primarily a bronchodilator action with minimal cardiac activity. The level of cyclic AMP can also be increased by decreasing its breakdown by the enzyme phosphodiesterase. The methylxanthines (theophylline) act by this mechanism.

The effects of beta-adrenergic agents (for example, isoproterenol) and the phosphodiesterase inhibitors (for example, theophylline) are synergistic, so that treatment with both of these classes of pharmacologic agents will result in less mediator release and less bronchospasm than one group alone.

The release of mediators may be prevented in some persons by administration of cromolyn sodium, even after the antigen antibody reaction has taken place.

Coincident with the biochemical information elucidating the method of action of bronchodilator agents have been studies of the dose response curves of theophylline preparations, correlating relief of airway obstruction with the serum levels of theophylline. Aminophylline, a salt of theophylline, given intravenously in a dose of 5.6 mg per kg of body weight as a loading dose and 0.9 mg per kg per hour as a maintenance dose, gives good plasma levels and bronchodilator activity in a large percentage of patients. There are also good studies available concerning the dose response of oral theophylline preparations.

Information is also available on the dose response curves of a variety of catecholamines given by aerosol (metaproterenol, isoetharine, isoproterenol, epinephrine). In addition, the beta-adrenergic agents metaproterenol and terbutaline are now available for oral use. Other agents are undergoing clinical trial and will, it is hoped, soon be available for clinical use.

An understanding of the pharmacology of bronchodilators can replace empiric therapy.

DONALD A. YOUNG, MD

REFERENCES

Orange RP, Austen KF: Chemical mediators of immediate hypersensitivity. Hospital Practice 6:79, Jan 1971

Mitenko PA, Ogilvie RI: Rational intravenous doses of theophylline. N Engl J Med 289:600-603, Sep 20, 1973

Gastrointestinal Endoscopy

ADVANCES IN gastrointestinal endoscopy have been rapid and dramatic since the development of flexible fiberoptic instruments in the late 1950's. The upper gastrointestinal tract to the level of the ligament of Trietz may now be inspected with a single instrument. In addition, cytological specimens may be obtained with the use of a brush or a pulsating jet of fluid introduced through a special channel in the endoscope, or a forceps may be introduced through the channel and a direct biopsy specimen taken. The instrument has also been utilized for therapeutic procedures, such as removal of gastric polyps, foreign bodies or retained sutures and arrest of bleeding by means of electrocoagulation or a laser beam.

An additional benefit is the ability to apply still photography and cinematography. In some centers, images are projected onto a television screen, thereby permitting viewing at a site remote from where the actual procedure is carried out. Detection of bleeding sites with endoscopy employing ultraviolet light after intravenous injection of fluorescein represents still another newer adaptation.

Endoscopic retrograde cholangio-pancreatography (ERCP) is now possible through the use of a side-viewing fiberoptic duodenoscope. A catheter introduced through the duodenoscope is inserted into the papilla of Vater under endoscopic guidance. Radiographic contrast material is then injected through the catheter and roentgenograms exposed to show the biliary or pancreatic ductal systems, or both. This nonoperative technique is of particular value in puzzling cases of jaundice and in the detection of pancreatic disease.

A long (165 cm) fiberoptic colonoscope is widely used today to visualize the entire large bowel. Through this instrument, biopsy specimens may be taken, cytological specimens obtained and polypoid lesions removed or destroyed by fulgur-